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**Evaluation of E-cadherin (CDH1) Gene Polymorphism Related To Gastric Cancer In Kurdish Population**

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**Abstract:** Helicobacter pylori (H.pylori) infection induces inflammation in gastric mucosa that may progress to gastric cancer that causes of much mortality. This cancer is a multistage process involved changes in environmental, genetic and epigenetic factors. Polymorphism in promoter of CDH1 gene is associated with reduced E-cadherin protein expression. Gastric cancer is associated with multiple changes nucleotides in CDH1 gene. **Aimed:** We were evaluating -160 (C>A) CDH1 gene polymorphism associations with gastric cancer in Kurdish population. **Methods:** A total of 306 biopsies taken from corpus of 144 gastric cancer patients and 162 nonulcer dyspepsia patients were classified as H.pylori-infected and H.pylori-uninfected. All diagnoses confirmed pathologically and molecularly. Polymorphism in -160(C>A) CDH1 was evaluated by PCR-RFLP. **Results:** Polymorphism of -160 (C>A) CDH1 in H.pylori-uninfected and H.pylori-infected groups were not associated with gastric cancer ( $p > 0.05$ ). Also there was not relationship between -160(C>A) CDH1 genotypes and H.pylori infection susceptibility ( $p > 0.05$ ). We found significant relationship between CC genotype and survival time among gastric cancer patients ( $p = 0.01$ ). **Conclusion:** -160(C>A) CDH1 polymorphism may regardless of presence or absence of H.pylori, don't influences gastric cancer sensibility in Kurdish population. In other hand CC genotype, as a good trait, increases period of life for Kurdish cancer patients.

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**Keywords:** E-cadherin, Kurdish population, polymorphism, Helicobacter pylori, CDH1 gene

**Introduction**

*H.pylori* is a spiral-shaped gram negative flagellate bacterium that colonizes the gastric mucosa of approximately 50 % of the world's population (1-3). *H.pylori* infection induces inflammation in gastric mucosa that involved in chronic gastritis (4-6). Gastritis may progress to other steps Such as, gastric atrophy, intestinal metaplasia, and gastric cancer (7, 8). Gastric cancer is causes of many mortality in America, however, over the past few decades rate of gastric cancer progress has fallen sharply in developed countries (9). Nevertheless, gastric cancer is a major cause of cancer result to death in developing countries, as after lung cancer remains the second highest cause of death in the world (10). Environmental factors play an important role in the risk of gastric cancer (11). This cancer is still the most common cause of gastric gland epithelium (9, 10). It has been established that gastric cancer is a multistage process involved changes in

environmental factors, genetic factors and epigenetic factors. Probable genetic risk factors such as single nucleotide polymorphisms (SNPs) in several pathways causing chronic inflammation of gastric mucosa and carcinogenesis in the next steps. The involved SNPs affect agents such as: pro-inflammatory cytokines, xenobiotic metabolizing enzymes, and growth factors (12-18). The study of these molecular pathways has helped to identify individuals at higher risk, particularly when examined with *H. pylori* infection and other environmental exposure (14, 15). Among genetic factors CDH1 is one of the most important tumor suppressor genes and is the good example of the potential tumor suppressor gene that is involved preferentially in cancer (19). Adhesion molecules, especially the calcium-dependent intercellular adhesion molecule E cadherin and its CDH1 gene (located on chromosome 16), play a central role in

carcinogenesis and metastasis (17, 20). The CDH1 gene encodes a transmembrane glycoprotein that mediates intercellular adhesion and cellular polarity. The E-cadherin protein is a tumor invasion suppressor, and loss of its function results in transition to an invasive phenotype in human epithelial cancers (17, 20). Polymorphisms in genes that increase the risk of cancer progression, including CDH1 gene is considerable. So that polymorphism in some regions of CDH1 gene increases the risk of cancer progression. Also some polymorphisms in promoter of CDH1 gene is associated with reduced E-cadherin protein expression (21). In the number of cancers dysfunction in regulation of CDH1 gene expression, particularly reduced expression of CDH1 gene, has been observed. There are many SNPs within or around the CDH1 gene that located in upstream gene and within promoter or in coding region. Example of these SNPs are +54 T> C, -160 C> A, -616 G> C and -3159 T> C that associated with transcription initiation (21). Gastric cancer is associated with multiple changes nucleotides in CDH1 gene (21). Many studies have found that different races have different polymorphisms of this gene that result in differ susceptibility of gastric cancer risk. Accordingly, we have chosen -160(C>A) polymorphism of CDH1 gene to examine any possible association with gastric cancer in Kurdish population (21).

### Subjects and methods

144 Kurdish patients with gastric cancer who underwent surgery at the first affiliated Hospital and cancer center of Kurdistan University of medical sciences, Kurdistan, Iran, were consecutively recruited from 2004 to 2009. All diagnoses were pathologically confirmed. The control series included 162 Kurdish nonulcer dyspepsia (NUD) who were undergoing upper gastrointestinal endoscopy. In both groups, cases and controls, *H.pylori* infection was determined by the UBT (Urease Breath Test) and PCR 16srRNA (22) on biopsies taken from the corpus. Patients were classified as *H.pylori* -infected only if the two tests were positive and *H.pylori*-uninfected if the two tests were negative, respectively. Demographic and clinical data were obtained from subjects through interview using a standard clinical pro forma. Survival data were obtained from a follow-up of the patients after surgery. Exclusion criteria included history of gastric neoplasm or surgery, liver disease, and previous treatment with nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics, or bismuth salts. Informed consents for participation were signed by all subjects. The study protocol was approved by the

Clinical Research Ethics Committee of the Kurdistan University of Medical Sciences.

### Histological examination

Sections of biopsy specimens were embedded 10 % buffered formalin and stained with hematoxylin and eosin to examine gastritis and with giemsa to detect *H.pylori* (23). The histological examination of gastric mucosa were blindly performed according to the Updated Sydney system (24).

### DNA isolation

DNA of gastric cancer patients was separated from paraffin embedded tumor tissues using QIAamp DNA Mini Kit (Qiagen, Germany). DNA of controls was extracted from biopsies taken from the corpus using Biospin Tissue genomic DNA Extraction Kit (Bio Flux, Japan). All extracted DNA was resuspended in UltraPure RNase/DNase-Free Distilled water.

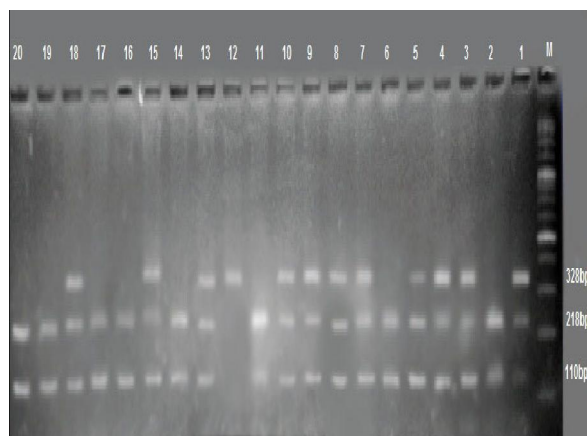
### Genotyping for -160 (C>A) CDH1 polymorphism

Genotyping analysis of -160 (C>A) CDH1 were performed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). Primer sequences for -160(C>A) variation of CDH1 gene are as follows: sense 5'-TGATCCCAG GTCTTAGTGAG-3', anti-sense 5'-AGTCTGAAGTACTTCCGCA-3'. The PCR amplification was performed in a total volume of 25 µL mixture containing: 100 ng genomic DNA, 1.0 mM of each primer, 200 mM of each dNTP, 2.0 mM of MgCl<sub>2</sub> and 1.0 U Taq DNA polymerase and 10 X Taq buffer (Fermentas) using the Biometra Tgradient 96 (Biometra, Germany). PCR conditions were as follows: denaturation at 95 °C for 5 min, followed by 35 cycles of 95 °C for 30 s, 58 °C for 30 s, and 72 °C for 30 s. A final extension was carried out at 72 °C for 5 min and cooling down to 4 °C. The PCR products were digested by restriction endonuclease *BesEI* (Fermentas), according to the manufacturer's instructions, at 37°C overnight and then separated by 3% agarose gel electrophoresis. Gel analysis was performed after staining with ethidium bromide. PCR products were shown to be digested into three types of fragments (Fig. 1). To confirm the genotyping results, selected PCR samples in both groups including samples of each genotype were re-genotyped by other laboratory personnel. There was no difference after sequencing the randomly selected samples.

### Statistical analysis

Data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL). Hardy-Weinberg equilibrium in all subjects was analyzed with the x<sup>2</sup> goodness-of-fit test before the ensuing analyses. The confounding effects of age and gender were adjusted using conditional logistic regression. Also Statistical

analysis was performed by non-paired t-test depending on the data set. Values of  $p < 0.05$  were considered as significant. Kaplan–Meier survival curves and the log-rank test for trend were used to evaluate the relationship between genotypes and the outcome of patients to the end of follow-up.



**Fig 1:** PCR-RFLP 3% agarose gel electrophoresis of the -160(C>A) CDH1 polymorphism indicating No.12 (AA = 328 bp) 1, 3, 4, 5, 7, 8, 9, 10, 13, 15, 18 (AC = 328, 218, 110 bp) 2, 6, 11, 14, 16, 17, 19, 20 (CC = 218, 110 bp) genotypes.

## Results

### Demographic and clinical characteristics

Genomic DNA was obtained among the 144 (44.4%) gastric cancer and 162 (55.6%) non-gastric cancer subjects then the DNA all subjects were genotyped. The demographic data of all subjects were demonstrated in Table 1. There was no significant difference between the two groups with respect to the age and gender distribution ( $p > 0.05$ ).

**Table 1:** Demographic data of study subjects.

Variable	Case (%)	Control (%)
<b>Overall</b>	144 (44.4%)	162 (55.6%)
<b>Gender</b>		
Male	81 (56.2%)	87 (53.7%)
Female	63 (43.8%)	75 (46.3%)
<b>Age Mean±SD (year)</b>	59.52 ±15	59.4 ±15.5

### -160(C>A) CDH1 polymorphism and susceptibility to gastric cancer

The frequencies of the polymorphism in cases and controls are shown in Table 2. Frequencies of -160(C>A) CDH1 genotypes in gastric cancer patients (CC, 52.8%; CA, 46.5% and AA, 0.7%) were compared with those in control subjects (CC, 58.8%; CA, 41.2% and AA, 0.0%). There was no significant

relationship between -160(C>A) CDH1 genotypes and susceptibility to gastric cancer.

**Table 2:** Adjusted 95% confidence intervals (CIs) for -160(C>A) CDH1 polymorphism in relation to gastric cancer

Genotype	Case (%)	Control (%)
<b>-160(C&gt;A) CDH1</b>		
AA	1 (0.7%)	0 (0.0%)
AC	67 (46.5%)	57 (41.2%)
CC	76 (52.8%)	105 (58.8%)
<b>#P value</b>		0.281

#  $p < 0.05$  was considered statistically significant.

### Evaluation of -160(C>A) polymorphism and susceptibility to H.pylori infection

In our population study -160(C>A) CDH1 genotypes evaluated in H.pylori-infected and H.pylori-uninfected population (Table 3). Genotypes of -160(C>A) CDH1 Compared in H.pylori-infected and H.pylori-uninfected subjects in case group ( $p = 0.778$ ) and control group ( $p = 0.44$ ). There was no significant relationship between -160(C>A) CDH1 genotypes and susceptibility to H.pylori infection.

**Table 3:** Adjusted 95% confidence intervals (CIs) for -160(C>A) CDH1 polymorphism and susceptibility to H.pylori infection

Genotypes of CDH1	H.pylori-infected (%)	H.pylori-uninfected (%)	#P value
<b>case</b>			
AA	0 (0.0%)	1 (0.7%)	0.778
AC	46 (31.9%)	21 (14.6%)	
CC	55 (38.2%)	21 (14.6%)	
<b>control</b>			
AA	0 (0.0%)	0 (0.0%)	0.44
AC	48 (44.4%)	9 (16.7%)	
CC	60 (55.6%)	45 (83.3%)	

#  $p < 0.05$  was considered statistically significant.

### Evaluation of -160(C>A) CDH1 polymorphism and survival of gastric cancer patients

Overall survival of the gastric cancer patients was analyzed using Kaplan–Meier survival curves for dependence on -160(C>A) CDH1 genotypes. There was significant difference among AC and CC genotypes in gastric cancer patients. According to the survival months gastric cancer patients with genotype of CC, live longer than gastric cancer patients with AC genotype after cancer (Table 4).

**Table 4.** Cox multivariate regression analysis of potential factors for overall survival in gastric cancer patients

-160(C>A) CDH1 Genotypes	Frequency	Survival (Months)
*AA	*	*
AC	51	18
CC	66	24.82
#P value		0.01

\*The sample size of AA was small so it was not statistically significant. #  $p < 0.05$  was considered statistically significant.

## Discussion

CDH1 gene located on chromosome 16 (1/22 q 16). The role of this gene is expression cellular adhesion proteins on epithelial cells. E-cadherin protein that resulting from expression of CDH1 gene, acts as a tumor suppressor (25). Mutations and impaired function of this gene has been found in gastric cancer (26). There is no data regarding CDH1 gene polymorphism on gastric cancer among Kurdish population till date. Since the CDH1 gene may play a major role in the development of gastric cancer, we studied polymorphism in the region promoter, -160 (C > A), of CDH1 gene to evaluate whether this polymorphism can affect the CDH1 gene in this population with gastric cancer. In the present study we found that frequencies of -160(C>A) CDH1 genotypes were not comparable in H.pylori-infected and H.pylori-uninfected subjects in both of case and control groups. These findings suggest that -160 (C>A) CDH1 polymorphism don't relate with H.pylori infection susceptibility. Also, we found that variants of -160(C>A) CDH1 were not associated with gastric cancer susceptibility in case and control groups. In other hand we observed gastric cancer patients with CC genotype have a longer survival than gastric cancer patients with AC genotype significantly. This result proposed CC as a good genotype in the process of cancer but not in gastric cancer susceptibility, in Kurdish population.

Molecular epidemiological studies evaluated the relationship between polymorphism of -160 (C>A) CDH1 gene and cancer. As a result, different cancers including: prostate, breast, colorectal and gastric cancer have different outcomes in different regions of the world. In a case-control study in the United Kingdom 433 patients with gastric cancer and 466 healthy controls were studied and finally declared that the genotype frequencies did not differ significantly between controls and patients, as a result, polymorphism of -160(C>A) CDH1 gene promoter was not associated with gastric cancer (27). In 2005, Lu Y et.al studied 206 gastric cancer patients and 261 healthy controls in China and finally

announced that -160 (C>A) CDH1 gene polymorphism may not have a major role in the development of gastric cancer in Chinese (28). In 2008, the French Jenab, et. al were investigated 245 gastric cancer patients and 950 control subjects. They determined there is no association between polymorphisms -160(C>A) in the CDH1 gene and gastric cancer (29). Chen B, et.al conducted a meta-analysis in China suggested that CDH1 gene polymorphic region of -160(C>A) don't have the role at increasing risk for gastric cancer (30). These results are consistent with our study but are inconsistent with the below studies.

In a study Yadong Wang, et.al in 2011 evaluated the polymorphism -160(C>A) CDH1 gene and the risk of colorectal cancer. In a result, this polymorphism was associated with increased risk for colorectal cancer (31). Another study in 2010 in Oman by AL. Moundir MS, et.al reported that the polymorphism in -160(C>A) CDH1 gene promoter is associated with increased risk for gastric cancer (32). Finally, we must acknowledge that the CDH1 gene polymorphism at position -160(C>A) has a various outcomes in different ethnic groups and geographic locations. This polymorphism should be evaluated with other environmental factors simultaneously. Therefore, further studies are needed to confirm our findings.

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